Tohoku J. Exp. Med., 2021, **253**, 61-68

Appendicular Skeletal Muscle Mass Correlates with Patient-Reported Outcomes and Physical Performance in Patients with Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF), an incurable lung disease of unknown cause, often presents with losses of skeletal muscle mass. IPF requires comprehensive care, but it has not been investigated which skeletal muscle mass index reflects holistic management factors: pulmonary function, patient-reported outcomes (PROs), and physical performance. We compared three representative indices of skeletal muscle mass with holistic management factors in IPF patients. Twenty-seven mild to severe IPF patients (21 male) with the mean age of 76.1 ± 5.9 years were enrolled. The three indices were appendicular skeletal muscle mass index (ASMI), cross-sectional area of pectoralis major (PM_{CSA}), and cross-sectional area of erector spinae muscles (ESM_{CSA}). ASMI is considered as a gold standard for sarcopenia assessment, while PM_{CSA} and ESM_{CSA} are frequently used in IPF. As PROs, we assessed breathlessness with the modified Medical Research Council dyspnea scale (mMRC), symptoms with the chronic obstructive pulmonary disease assessment test (CAT), and health-related quality of life with St. George's Respiratory Questionnaire (SGRQ). For physical performance, peripheral muscle strength and 6-min walk distance (6MWD) were investigated. In this cross-sectional study, ASMI showed the greatest number of significantly correlated indices, such as pulmonary function, peripheral muscle strength, 6MWD, mMRC, and SGRQ. PM_{CSA} showed the next greatest number of correlations, with peripheral muscle strength, 6MWD, and mMRC, whereas ESM_{CSA} showed no significant correlations with any index. Thus, ASMI correlated with both PROs and physical performance, and PM_{CSA} correlated mainly with physical performance. In conclusion, assessing ASMI is helpful for the comprehensive care of patients with IPF.

Keywords: cross-sectional area; erector spinae muscle; pectoralis major muscle; sarcopenia; 6-minute walk distance
Tohoku J. Exp. Med., 2021 January, **253** (1), 61-68.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common chronic and progressive interstitial lung disease (ILD) of unknown cause (Lederer and Martinez 2018). IPF patients often present with progressive loss of muscle mass and strength, which has gained attention as sarcopenia (Cruz-Jentoft et al. 2010; Suzuki et al. 2018). If no specific cause other than aging is evident, the sarcopenia is considered 'primary.' Conversely, sarcopenia is considered 'secondary' when causal factors other than or in addition to aging are evident (Cruz-Jentoft et al. 2010). Whether primary or secondary, sarcopenia is associated with a risk of adverse outcomes, such as disability, poor quality of life (QOL), and death in elderly people (Cruz-Jentoft et al. 2010; Fielding et al. 2011).

Among the many modalities used to quantify skeletal muscle mass in sarcopenia assessment, appendicular skeletal muscle mass index (ASMI) as measured by dual-energy X-ray absorptiometry (DXA) has continued to be the gold

Received August 12, 2020; revised and accepted December 28, 2020. Published online January 21, 2021; doi: 10.1620/tjem.253.61.
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standard, and has been recognized as significantly associated with physical disability and QOL in the general elderly population (Baumgartner et al. 1998; Buckinx et al. 2018). This modality is commonly used because of the low exposure to radiation, its accuracy, and its clinical feasibility (Cruz-Jentoft et al. 2010; Fielding et al. 2011; Heymsfield et al. 2015).

To the best of our knowledge, no studies have quantified skeletal muscle mass in patients with IPF using DXA. On the other hand, measurement of the cross-sectional area (CSA) of skeletal muscles such as the erector spinae muscle (ESM_{CSA}) and pectoralis muscle (PM_{CSA}) on single-slice axial computed tomography (CT) is frequently used to assess skeletal muscle mass in patients with IPF, because assessment of these muscles does not require additional radiation exposure (Suzuki et al. 2018; Moon et al. 2019; Nakano et al. 2020; Awano et al. 2020). Several recent reports have focused on ESM_{CSA} as related to mortality in patients with IPF (Suzuki et al. 2018; Nakano et al. 2020; Awano et al. 2020).

Current protocols for IPF management recommend multidisciplinary team meetings, not only to ensure diagnostic accuracy, but also to determine the therapeutic options to achieve a comprehensive care approach that includes pharmacological and nonpharmacological treatments, palliative care, patient education, and increased support throughout the course of the disease (Raghu et al. 2011). Patient-reported outcomes (PROs), such as questionnaires or surveys that ask patients for their perceptions about issues like symptoms being experienced or QOL, play key roles in the multifaceted symptomatic management of patients (Kalluri et al. 2020). In addition, programs involving supervised pulmonary rehabilitation, as a pivotal component of comprehensive management, are driven by regular physical assessments from therapists (Spruit et al. 2013).

The management of IPF should thus rely not only on prognostic factors, but also on holistic factors such as PROs and physical performance. However, to date, it has not been investigated which skeletal muscle mass assessment is appropriate from the perspective of comprehensive management of IPF patients. The purpose of this study was to investigate which of three skeletal muscle mass indices (ASMI, ESM_{CSA} and PM_{CSA}) is most correlated with factors representing the patient condition of IPF, including PROs and physical performance.

Materials and Methods

Subjects

Eligible patients were recruited from IPF patients as a subgroup of patients recruited for the Toho Rehabilitation for Interstitial Pneumonia (TRIP) study from July 2014 to July 2017. The TRIP study is investigating the long-term effects (2 years of follow-up) of pulmonary rehabilitation on patients with chronic interstitial lung diseases due to any cause, and is still ongoing at Toho University Omori Medical Center, Tokyo, Japan (Igarashi et al. 2018). The Toho University Omori Medical Center Ethics Committee approved the study (approval #27-82).

Exclusion criteria were: inability to complete a 6-minute walk test (6MWT) due to any reason; unstable cardiac disease; active cancer; severe orthopedic or neurological disorder that limited exercise performance; or inability to complete the questionnaire. During the study period, 80 stable IPF patients who met the inclusion criteria were referred to the TRIP rehabilitation program, and 27 patients who agreed to and underwent DXA were analyzed. IPF was diagnosed by a multidisciplinary discussion according to the American Thoracic Society/European Respiratory Society statement (Raghu et al. 2011).

At the time of patient referral to the rehabilitation department, demographic data, pulmonary function indices, physical performance indices, and PROs were assessed. Both DXA and CT were performed within 2 weeks of these assessments.

Pulmonary function testing

Pulmonary function tests included spirometry, total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLco), and respiratory muscle strengths and blood gas analysis.

Forced vital capacity (FVC), forced expiratory volume in 1.0 s (FEV_1), FEV_1/FVC ratio, TLC, and DLco were assessed using CHESTAC-8900 (DN) (CHEST, Tokyo, Japan). TLC was defined by the helium concentration reaching equilibrium. DLco was measured with the maneuver for the single-breath diffusing capacity, started with unforced exhalation to residual volume, followed by rapid inhalation to TLC.

To assess respiratory muscle strength, mouth pressures were measured at residual volume for maximal inspiratory mouth pressure (PImax) and at total lung capacity for maximal expiratory mouth pressure (PEmax) in sitting position using a Multi-Functional Spirometer HI-801 (CHEST). All participants were seated with nose clips on and sharp, forceful effort was maintained in each test for a minimum of 3 s.

For arterial blood gas analysis, a 1.5-mL sample of blood was drawn from the radial artery in subjects sitting upright at rest and was analyzed in duplicates using an ABL800 FLEX blood gas analyzer (Radiometer, Copenhagen, Denmark) within a few minutes.

Physical performance assessments

Physical performance was assessed by leg muscle strength, handgrip strength, and 6MWT.

Leg muscle strength was assessed as quadriceps muscle force estimated by measuring isometric knee extension strength with a hand-held dynamometer (a Mobie; Sakai Medical Corp., Tokyo, Japan). Patients sat on a training bench and adjusted the position of the gluteal region so that a bench leg was behind the lower extremity on the measurement side (Igarashi et al. 2018).

Handgrip strength was assessed for each hand with the shoulder and wrist in neutral positions (Igarashi et al. 2018). Measurements were performed three times for each hand, taking the largest value as grip strength.

The 6MWT was performed according to published international guidelines (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). Patients were instructed to walk as far as possible along a 30-m corridor in 6 min with continuous monitoring of oxygen saturation and heart rate. All patients had performed at least one test prior to entry into the study to exclude any training effect in the 6-minute walk distance (6MWD).

Patient-reported outcomes

Patient-reported outcomes were based on assessment of breathlessness, symptoms, and health-related QOL (HRQOL). Breathlessness was evaluated using the 5-grade modified Medical Research Council dyspnea scale (mMRC). Symptoms and HRQOL were evaluated using the chronic obstructive pulmonary disease assessment test (CAT) and St. George's Respiratory Questionnaire (SGRQ), respectively (Nagata et al. 2012). Although initially developed for patients with chronic obstructive pulmonary disease, both the CAT and SGRQ have been validated in patients with ILD (Nagata et al. 2012).

Severity assessment

Severity of IPF was assessed using both Japanese Respiratory Society (JRS) criteria and the Gender-Age-Physiology (GAP) index. JRS criteria classified IPF using the arterial oxygen tension (PaO_2) at rest and minimum SpO_2 during the 6MWT (Arai et al. 2014). GAP index is a staging system based on sex, age, FVC, and DLco. The GAP index has been reported as a clinical prognostic factor associated with outcomes in patients with IPF (Ley et al. 2012). In this study, both GAP score (summation of each point) and GAP stage were used.

Assessment of skeletal muscle mass

Whole-body DXA (Lunar iDXA; GE Healthcare, Madison, WI, USA) was performed to assess body composition by certified radiological technologists, according to the standard operating method (Cruz-Jentoft et al. 2010; Heymsfield et al. 2015). Whole-body and four-limb muscle masses were calculated as the fat-free mass minus the bone mass. Appendicular skeletal muscle mass (ASM) was calculated as the sum of the muscle mass of the arms and legs, as a good proxy for whole-body skeletal muscle mass (Kim et al. 2002). To account for the potential influence of body size or height, appendicular skeletal muscle mass in kilograms was divided by the height in meters squared as the ASMI, one of the most widely used indices for assessment of sarcopenia (Cruz-Jentoft et al. 2010; Fielding et al. 2011).

CSA of skeletal muscles from CT

CT was performed for 1- to 5-mm-thick samples at slice intervals of 1-5 mm using SOMATOM Definition Flash, SOMATOM Definition AS+, or SOMATOM Definition Edge (SIEMENS, Munich, Germany). All images were collected as Digital Imaging and Communications in Medicine (DICOM) data, which were then converted into a compact disc read-only memory for input into electronic medical records.

For quantitative analysis of skeletal muscles, CT images were reconstructed using the mediastinal setting. We analyzed single-slice axial CT taken at the lower margin of the 12th thoracic vertebra to measure ESM_{CSA}, in accordance with previous reports (Tanimura et al. 2016; Suzuki et al. 2018; Nakano et al. 2020; Awano et al. 2020). For quantitative assessment of the PM_{CSA}, the superior aspect of the aortic arch and then the first axial slice above the arch were identified, as described previously (Tanimura et al. 2016; Awano et al. 2020).

The quantitative analysis of images was performed using the ImageJ processing system freely available from the National Institute of Health (https://imagej.net/Welcome, accessed April 27, 2020). Anonymized data in DICOM format were opened using ImageJ software (Jones et al. 2015). Bilateral ESMs and PMs were identified and manually shaded using a predefined attenuation range of −29 to +150 Hounsfield units. The observer outlined the

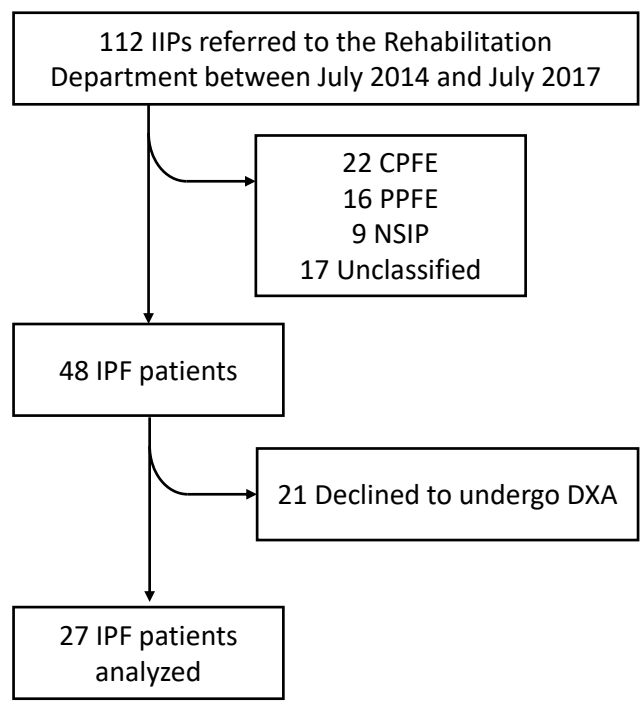

Fig. 1. Flowchart of patient recruitment in this study.
IIPs, idiopathic interstitial pneumonias; PPFE, pleuroparenchymal fibroelastosis; CPFE, combined pulmonary fibrosis and emphysema; NSIP, nonspecific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; DXA, dual-energy X-ray absorptiometry.

Table 1. Patient characteristics.

	IPF (n = 27)
Age, years	76.1 ± 5.9
Sex, n (%)	
Male	21 (78)
Height, cm	158.9 ± 8.6
Weight, kg	60.7 ± 9.8
BMI, kg/m^2	24.0 ± 3.0
Severity	
JRS, (I/II/III/IV)	2.3 ± 1.2 (11/2/9/5)
GAP index (I/II/III)	1.9 ± 0.6 (7/16/4)
GAP score	4.3 ± 1.3
Pulmonary function	
FVC, L	2.1 ± 0.6
FVC, % predicted	72.0 ± 17.1
FEV_1, L	1.7 ± 0.5
FEV1, % predicted	94.2 ± 28.1
FEV_1/FVC, %	85.0 ± 7.4
TLC, L	3.4 ± 0.9
DL_{co}, % predicted	58.4 ± 18.2
PEmax, cmH_2O	91.7 ± 23.1
PImax, cmH_2O	75.1 ± 21.0
pH	7.4 ± 0.0
PaO_2, mmHg	78.6 ± 13.5
$PaCO_2$, mmHg	40.6 ± 3.8
Serum IP marker	
KL-6, U/mL	1,130 ± 679
SP-A, ng/mL	70.4 ± 37.8
SP-D, ng/mL	293.3 ± 195.6
Skeletal muscle assessment	
ASMI, kg/m^2	7.1 ± 1.0
PM_{CSA}, cm^2	26.6 ± 8.8
ESM_{CSA}, cm^2	28.9 ± 9.6
Physical assessment	
Quadriceps force, nm/kg	1.24 ± 0.4
Handgrip strength, kg	26.2 ± 6.4
6MWT	
6MWD, m	350.0 ± 89.3
Lowest SpO_2, %	86.2 ± 4.4
Patient-reported outcomes	
mMRC, (0/1/2/3/4)	1.4 ± 1.1 (7/7/9/3/1)
CAT	12.9 ± 7.7
SGRQ	
Symptoms	34.8 ± 17.6
Activity	47.4 ± 25.0
Impacts	27.5 ± 21.9
Total	34.8 ± 20.3

The values are mean ± SD.
BMI, body mass index; JRS, Japanese Respiratory Society; GAP, Gender-Age-Physiology; FVC, forced vital capacity; FEV1, forced expiratory volume in 1.0 second; TLC, total lung capacity; DLco, diffusing capacity of the lung for carbon monoxide; PEmax: maximal expiratory pressure; PImax: maximal inspiratory pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; IP, interstitial pneumonia; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein A; SP-D, surfactant protein D; ASMI, appendicular skeletal muscle mass index; PM_{CSA}, cross-sectional area of pectoralis major muscle; ESM_{CSA}, cross-sectional area of erector spinae muscle; 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; mMRC, modified British Medical Research Council questionnaire; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire.

muscles and the software calculated the surface area within the limits of the drawn boundary. ESM_{CSA} and PM_{CSA} were presented as the sum of bilateral muscle areas. Measurement of skeletal muscles was independently performed by two researchers (K.E. and S.E.), who were blinded to clinical data.

Statistical analysis

Spearman's rank correlation was used to examine relationships between ASMI and PM_{CSA} or ESM_{CSA}. Data are expressed as mean ± standard deviation. The significance level was set at $p < 0.05$. All analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

Results

Between July 2014 and July 2017, a total of 112 patients with idiopathic interstitial pneumonia (IIP) were referred to the Rehabilitation Department. The underlying pathology was IPF in 58 patients, combined pulmonary fibrosis and emphysema (CPFE) in 22 patients, pleuroparenchymal fibroelastosis (PPFE) in 16 patients, nonspecific interstitial pneumonia (NSIP) in 9 patients, and unclassified IIP in 17 patients. Among the 58 patients with IPF, 21 patients declined to undergo DXA and were excluded. We therefore analyzed data from a final total of 27 IPF patients using the MDD approach (Fig. 1).

Table 1 shows patient characteristics for these subjects. Mean age was 76.1 ± 5.9 years, and GAP stage was I in 26%, II in 59%, and III in 15%. Mean FVC was 2.1 ± 0.6 L, representing 72.0 ± 17.1% of the predicted value.

Table 2 shows the correlation coefficient between each index and ASMI, PM_{CSA}, and ESM_{CSA}. ASMI showed the greatest number of significantly correlated indices, such as weight ($r = 0.56$, $p < 0.01$), body mass index (BMI) ($r = 0.48$, $p < 0.05$), FVC ($r = 0.47$, $p < 0.05$), PEmax ($r = 0.63$, $p < 0.01$), peripheral muscle strength ($r = 0.49$, $p < 0.01$), 6MWD ($r = 0.57$, $p < 0.01$), mMRC ($r = -0.57$, $p < 0.01$), and SGRQ ($r = -0.48$. $p < 0.01$). This was followed by PM_{CSA}, which showed significant correlations with age ($r = -0.41$, $p < 0.05$), weight (0.53, $p < 0.01$), PEmax ($r = 0.60$, $p < 0.01$), peripheral muscle strength ($p < 0.01$), 6MWD ($r = 0.64$, $p < 0.01$), and mMRC ($r = -0.46$, $p < 0.05$). On the other hand, ESM_{CSA} showed no significant correlations with any index.

Fig. 2 shows the relationship between ASMI and

Table 2. Correlation coefficients between skeletal muscle assessments and indices of disease progression.

	ASMI	PM_{CSA}	ESM_{CSA}
Age, years	–0.15	–0.41*	0.08
Height, cm	0.23	0.38	0.10
Weight, kg	0.56**	0.53**	–0.08
BMI, kg/m^2	0.48*	0.33	–0.15
Severity			
JRS	–0.11	–0.20	0.06
GAP index	–0.21	–0.06	–0.13
GAP score	–0.18	–0.06	–0.17
Pulmonary function			
FVC, L	0.47*	0.35	0.14
FVC, % predicted	0.08	–0.03	0.11
FEV_1, L	0.34	0.25	0.14
FEV1, % predicted	0.06	–0.12	0.10
FEV_1/FVC, %	–0.30	–0.29	0.17
TLC, L	0.25	0.19	0.11
DL_{co}, % predicted	0.16	0.04	0.17
PEmax, cmH_2O	0.63**	0.60**	0.07
PImax, cmH_2O	0.24	0.14	–0.17
pH	0.02	–0.01	0.01
PaO_2, mmHg	0.39	0.33	0.19
$PaCO_2$, mmHg	–0.21	–0.15	0.01
Serum IP marker			
KL-6, U/mL	–0.01	0.08	–0.13
SP-A, ng/mL	–0.15	–0.28	–0.07
SP-D, ng/mL	–0.30	–0.22	–0.14
Physical assessment			
Quadriceps force, nm/kg	0.49**	0.50**	0.22
Handgrip strength, kg	0.49**	0.59**	–0.10
6MWT			
6MWD, m	0.57**	0.64**	–0.01
Lowest SpO_2, %	0.14	0.33	0.03
Patient-reported outcomes			
mMRC	–0.57**	–0.46*	0.09
CAT	–0.19	–0.01	0.02
SGRQ			
Symptoms	–0.35	–0.19	–0.10
Activity	–0.42*	–0.37	–0.20
Impacts	–0.50**	–0.33	–0.30
Total	–0.48*	–0.36	–0.28

BMI, body mass index; JRS, Japanese Respiratory Society; GAP, Gender-Age-Physiology; FVC, forced vital capacity; FEV1, forced expiratory volume in 1.0 second; TLC, total lung capacity; DLco, diffusing capacity of the lung for carbon monoxide; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; IP, interstitial pneumonia; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein A; SP-D, surfactant protein D; ASMI, appendicular skeletal muscle mass index; PM_{CSA}, cross-sectional area of pectoralis major muscle; ESM_{CSA}, cross-sectional area of erector spinae muscle; 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; mMRC, modified British Medical Research Council questionnaire; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire.
*$p < 0.05$; **$p < 0.01$.

PM_{CSA} or ESM_{CSA}. A strong correlation existed between ASMI and PM_{CSA} ($r = 0.88$, $p < 0.01$), whereas no significant correlation was seen between ASMI and ESM_{CSA} ($r = -0.06$, $p = 0.76$).

Discussion

This appears to be the first report to quantify skeletal muscle mass in patients with IPF using DXA, a gold-standard method for quantifying muscle mass. This cross-sectional study found that ASMI from DXA correlated better with many outcome measures in IPF than CSA of a single muscle from single-slice axial CT. Between two CSAs of muscles (PM_{CSA} and ESM_{CSA}), PM_{CSA} correlated better with physical performance.

Subjects in this study were older (mean age, 76.1 years) than subjects in the studies by Suzuki et al. (2018) (mean, 69.0 years), Nakano et al. (2020) (mean, 65.9 years), or Awano et al. (2020) (median, 66 years), each of which showed the significance of ESM_{CSA} as a strong predictor of mortality in IPF patients. Accordingly, our ESM_{CSA} (mean, 28.9 cm^2) was smaller than those reported by Suzuki et al. (2018) (mean, 32.8 cm^2), Nakano et al. (2020) (mean, 34.2 cm^2), and Awano et al. (2020) (median, 30.7 cm^2). These differences in results could be attributable to age-related changes.

Although sarcopenia is considered 'secondary' when causal factors other than ageing are evident (Cruz-Jentoft et al. 2010), no distinctions have been made in recommendations for methods or cut-offs to distinguish between primary and secondary sarcopenia. Usually, in elderly individuals with chronic diseases, overlap between primary and secondary sarcopenia can be expected. Skeletal muscle dysfunction has been well investigated in chronic obstructive pulmonary disease (COPD) among respiratory diseases (Maltais et al. 2014). In COPD, a shift in the distribution of fiber types from type I to type II is a typical feature of skeletal muscle (Maltais et al. 2014). The reduction of muscle mass with disease progression in the erector spinae muscle, as a muscle with predominantly type I fibers (Zhu et al. 1989), appears to be a reasonable phenomenon in this context. Since a transition of muscle fibers from type II to type I occurs with aging (Cruz-Jentoft et al. 2010), sarcopenia in COPD patients seems to be more disease-related than age-related.

On the other hand, the fiber types of skeletal muscles in patients with IPF have not been reported previously. Our study showed that ASMI and PM_{CSA} correlated with indices of disease progression. Since the pectoralis major muscle predominantly consists of type I fibers which are vulnerable to aging, sarcopenia in IPF patients could be more age-

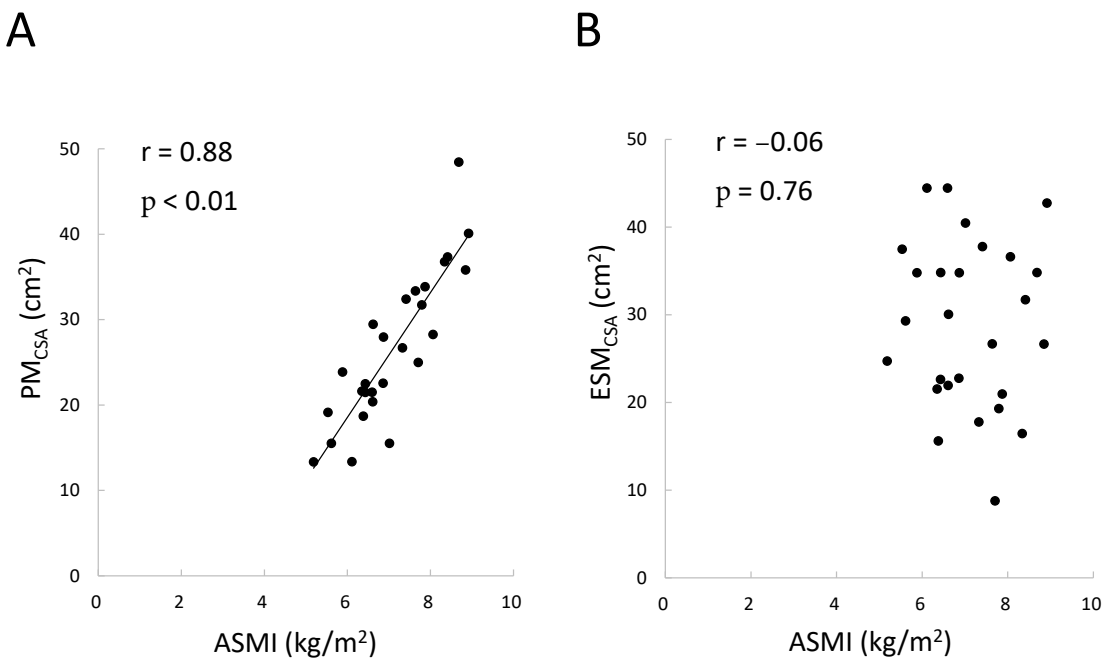

Fig. 2. Relationships between ASMI and either PM_{CSA} or ESM_{CSA}.
A) Significant relationship between ASMI and PM_{CSA} in 27 patients with IPF. B) No relationship between ASMI and ESM_{CSA} in 27 patients with IPF.
ASMI, appendicular skeletal muscle mass index; PM_{CSA}, cross-sectional area of pectoralis major muscle; ESM_{CSA}, cross-sectional areas of erector spinae muscle.

related than disease-related. Further studies including histopathological studies of the skeletal muscles of IPF patients are warranted.

Because of the need for CT, PM_{CSA} and ESM_{CSA} are mainly investigated in patients presenting with respiratory disease. In patients with COPD, small PM_{CSA} has been associated with airway obstruction, worsened results from SGRQ and mMRC, and declines in 6MWD (McDonald et al. 2014). Smaller ESM_{CSA} was also associated with airway obstruction and worsened SGRQ and mMRC (Tanimura et al. 2016), but associations between ESM_{CSA} and 6MWD have not been reported in COPD. Low ASMI has been associated with airway obstruction and worsened mMRC (Hwang et al. 2017; Han et al. 2019), but associations between ASMI and 6MWD or SGRQ have not been reported in COPD. The roles of ASMIs thus need to be elucidated in COPD.

Since COPD is a systemic inflammation that induces systemic muscle wasting, ASMI conceivably decreases with disease progression. However, muscle wasting occurs systemically in older people as a physiological response to fasting, malnutrition, or inactivity. Malnutrition has been identified in nearly one-third of IPF patients (Jouneau et al. 2019). IPF patients have also been reported as significantly inactive compared with age-matched healthy individuals (Nishiyama et al. 2018). In addition, common comorbidities of IPF such as diabetes and renal and cardiac failure induce muscle wasting (Cohen et al. 2015). Patients with IPF are thus vulnerable to systemic muscle wasting. Since systemic muscle wasting due to both malnutrition and inactivity are known to relate to poor QOL and physical performance (Fielding et al. 2011), low ASMI could conceivably be related to poor HRQOL and low ratings for physical assessment in patients with IPF.

This study appears to be the first to evaluate the relationship between skeletal muscle mass and HRQOL in patients with IPF. ASMI correlated significantly with SGRQ, unlike either PM_{CSA} or ESM_{CSA} (Table 2). The progression of primary sarcopenia is known to correlate with the decline in HRQOL among the elderly (Beaudart et al. 2015). ASMI is a recommended assessment of skeletal muscle mass for sarcopenia, so it may make sense that ASMI correlated significantly with SGRQ in patients with IPF.

Care given to patients with IPF should be multifaceted and multidisciplinary, and should attempt to improve patient QOL while slowing declines in lung function (Raghu et al. 2011; Kalluri et al. 2020). Under such approaches, PROs such as HRQOL and self-rating dyspnea scales provide clues to understanding what patients with IPF are actually experiencing and how that experience affects any number of life domains. In our study, ASMI correlated well with PROs, suggesting that measurement of ASMI might be important for patient-centered care in IPF management.

Pulmonary rehabilitation has been shown to provide short-term benefits with regard to dyspnea, functional capacity, and QOL, and is recommended in international

treatment guidelines (Raghu et al. 2011). Since the cornerstones of pulmonary rehabilitation are exercise training, resistance training, flexibility training, and advice on breathing techniques, assessing the physical performance of patients is important to tailor the rehabilitation program to the individual (Spruit et al. 2013). In this study, both ASMI and PM_{CSA} correlated well with parameters of physical performance such as PEmax, quadriceps force, handgrip strength, and 6MWD (Table 2), suggesting that PM_{CSA} is equivalent to ASMI in physical assessment. Actually, ASMI and PM_{CSA} correlated very well, whereas ESM_{CSA} did not (Fig. 2).

In patients with IPF, ASMI and PM_{CSA} correlated significantly with physical performance, which is an important element of sarcopenia (Cruz-Jentoft et al. 2010). This suggests that these indices are better than ESM_{CSA} for assessing sarcopenia in patients with IPF. Given this result, the pulmonary rehabilitation program should potentially include resistance training of the upper limb to prevent sarcopenia in patients with IPF. However, further interventional studies are warranted to clarify this point.

In conclusion, ASMI correlated well with both PROs and physical performance in patients with IPF. PM_{CSA} correlated with physical performance in patients with IPF, whereas ESM_{CSA} did not correlate with any of the indices of disease progression investigated in the study. Our results show the usefulness of monitoring ASMI for comprehensive management by an interdisciplinary team of IPF patients.

Acknowledgments

This study was partly supported by JSPS KAKENHI Grant Numbers 19H03984 and 19K22821. We wish to thank the study subjects for allowing the use of their personal data. We would also like to thank FORTE Science Communications (https://www.forte-science.co.jp/) for English language editing.

Author Contributions

S.E. conceived the study design and wrote the manuscript. K.E. analyzed the data and participated in the study design and discussion. K.E., Y.I., K.Y., A.T., N.S., Y.U., and Y.N. collected the data and participated in the discussion. K.K. and S.H. finalized the manuscript. All authors reviewed and approved the manuscript.

Conflict of Interest

The authors declare no conflict of interest. On the other hand, S.H. belongs to an endowed department sponsored by Nippon Boehringer Ingelheim Co., Ltd., Shionogi & Co., Ltd., Chugai Pharmaceutical Co., Ltd. and Teijin-Pharma Co., Ltd.

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